B1 14. (Once Amended) The lyophilizate of claim 13, wherein the lyophilizate is essentially free of [polyethylene glycols and/or proteinaceous pharmaceutical auxiliary additives] additional proteins.

B2 16. (Once Amended) The lyophilizate of claim 13, further comprising a buffering agent or an isotonizing agent which is present in an amount such that a reconstituted solution of the lyophilizate has a pH value of 5-8.

REMARKS

Claims 13-36 are currently pending. In this Response, applicants amend claims 13, 14 and 16.

Claims 14, 16-18, 25, 28, 31, 32 and 34 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claims 17 and 18 are objected to for the recitation "at least three months". The Examiner objects to the lack of an upper limitation in this term.

Applicants submit that the Examiner's objection is completely misplaced. The specification need not recite an upper limit in this regard. The term "at least three months" would be well understood by those of skill in the art as meaning that the lyophilizate of the claims must be storage-stable for at least three months, but can be storage-stable for any further amount of time and come within the scope of the claims. The Examiner must analyze indefiniteness not only by the content of the disclosure, but also by the claim interpretation that would be understood by one possessing the ordinary level of skill in the

art at the time the invention was made. See MPEP §2173.02. Applicants cannot believe that one of ordinary skill in the art would not be well apprised of the meaning of "at least three months".

The Examiner also objects to claims 17 and 18 because of the term "of about".

This rejection is respectfully traversed.

There are a large number of cases which hold that the term "about" is not indefinite. Applicants cannot understand why this rejection was made. See, for example, MPEP §2173.05(b).

The Examiner objected to claims 31 and 32 because of the term "up to". Applicants also cannot understand why this rejection was made. Those of skill in the are would be well apprised that the term "up to" means that the composition of the claims can contain the recited amount, and no more, and may contain less than the recited amount. Applicants inquire as to what is vague and indefinite about the term.

The Examiner objects to claims 28 and 34 for the recitation "physiologically acceptable". The rejection of this term is simply absurd. A brief query on the U.S. Patent and Trademark Office database indicate that 371 patents have issued in 1999-2000 with the term "physiologically acceptable". Thus, it is quite clear that one of skill in the art would be well apprised as to the meaning of this phrase.

Claim 14 is considered vague and indefinite for the term "proteinaceous pharmaceutical auxiliary additives". The Examiner notes that the specification indicates that serum albumins come within this term, but it cannot be determined what other molecules are included. The Examiner inquires as to whether the amino acids listed in the claims are within the scope of this term.

Applicants submit that the objection has been overcome due to applicants changing the term "proteinaceous pharmaceutical auxiliary additives" to "additional proteins". The preferred lyophilizate includes no other protein material besides the monoclonal antibody or polyclonal antibody. The amino acids contained in the lyophilizate are monomeric, and therefore could not be considered to be a protein.

Claim 16 is considered vague and indefinite for the term "isotonizing" agent. The Office Action states that the specification does not clearly define what can be included or excluded as an isotonizing agent nor as a buffering agent.

Applicants note that page 13, first full paragraph, indicates that the lyophilizate may contain auxiliary substances such as buffers or isotonizing agents to adjust the pH value to 5-8, preferably 6.0-7.4. Applicants have indicated the function of the buffering agent or isotonizing agent in order to overcome the Examiner's objection. Specifically, claim 16 now indicates that the buffering agent or isotonizing agent is present in an amount such that a reconstituted solution of the lyophilizate has a pH value of 5-8.

Claim 25 is considered vague and indefinite for the recitation "monomer unit".

Applicants respectfully submit that this objection is misplaced because the phrase "a molecular weight of 50-200 kDa per monomer unit" clearly specifies the size of the antibodies encompassed by the claim. As the Examiner must know, monoclonal antibodies are known to aggregate into dimers, trimers, etc. The limitations of claim 25 merely indicate that the molecular weight is to be determined on a monomer basis.

Claims 13, 15, 16, 19, 20, 23-25, 27, 28 and 34 are rejected under 35 U.S.C. §102(b) as being anticipated by Chuntharapai et al. (U.S. Patent No. 5,440,021).

Chuntharapai et al. is concerned with the manufacture of the recombinantly produced IL-8 type B-receptor for the preparation and purification of antibodies capable of binding to the receptor. The antibodies are also used in the prevention and treatment of inflammatory conditions. Column 24, lines 44-66, disclose therapeutic compositions containing the antibodies. Among the listed ingredients for the lyophilizate are surfactants such as polyethylene glycol. See column 24, line 65.

An object of the present invention is to avoid the use of polymers such as polyethylene glycol. In order to make this feature more clear, applicants have incorporated a limitation previously contained in claim 14 (that the lyophilizate is essentially free of polyethylene glycol) into claim 13. Applicants note that a similar amendment is not necessary with regard to claim 27, since this claim is directed to a lyophilizate consisting essentially of a certain number of components, whereby polyethylene glycols are excluded.

Applicants respectfully submit that the rejection over Chuntharapai should be withdrawn.

Claims 13-24 and 26-36 rejected under 35 U.S.C. §103(a) as being unpatentable over Chuntharapai in view of Michaelis et al. (U.S. Patent No. 5,919,443) in further view of Phillips et al. (WO 89/11297). The Examiner admits that Chuntharapai et al. does not teach a lyophilizate which is essentially free of polyethylene glycols and/or proteinaceous pharmaceutical auxiliary additives, and/or which meets the additional limitations of claims 17, 18, 21, 22, 26, 29-33, 35 and 36. The Examiner relies on Michaelis et al. as teaching a lyophilizate which is essentially free of polyethylene glycols and/or proteinaceous pharmaceutical auxiliary additives and contains the further limitations of the rejected

claims. Phillips is relied upon as teaching that, as of 1989, the lyophilization of therapeutic antibodies was art-known.

The Examiner takes the position that it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Chuntharapai, Michaelis and Phillips.

Chuntharapai has been discussed above. As noted, the object of this invention is to identify and prepare antibodies to the IL-8 type B-receptor. The invention of Chuntharapai is therefore neither concerned with stability problems nor problems of avoiding polyethylene glycols and/or additional proteins in the formulations disclosed therein. The Chuntharapai reference mentions possible formulations suitable for the disclosed antibodies only generically; thus, this patent could not possibly provide the motivation to prepare new and stable formulations which do not include several ingredients (i.e., polyethylene glycols and/or additional proteins) specifically mentioned therein.

Michaelis is concerned with formulations and their stabilization; however, this patent is not at all concerned with monoclonal and/or polyclonal antibodies, as are found in the present invention. Rather, Michaelis is concerned with the stabilization of G-CSF. As the Examiner must know, monoclonal and polyclonal antibodies are chemically completely different from G-CSF; thus, a person of ordinary skill in the art could not expect that a formulation which stabilizes G-CSF can also have stabilizing effects on monoclonal and polyclonal antibodies.

In order to establish a *prima facie* case of obviousness, the closest prior art must be identified and, starting from this document, it must be determined whether one of ordinary skill in the art would have obtained the present invention by combining the closest prior art with further documents and/or common general knowledge.

In the present case, the Examiner seems to take the position that the closest prior art is Chuntharapai. However, applicants respectfully submit that this patent is not the closest art, because this document is not at all concerned with stabilization problems and does not provide any particular information about formulations which could stabilize monoclonal or polyclonal antibodies without the use of polyethylene glycols. While, as noted above, Michaelis does deal with stabilization problems, this document relates to the stabilization of G-CSF, and not monoclonal or polyclonal antibodies. One of ordinary skill in the art would not have combined Michaelis and Chuntharapai, since the former document is not at all concerned with stability while the latter document is not at all concerned with monoclonal or polyclonal antibodies. This combination would not have been made without the benefit of hindsight.

Applicants respectfully submit that the rejection should be withdrawn.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper.

Respectfully submitted,
Arent Fox Kintner Plotkin & Kahn

Richard J. Berman
Attorney for Applicant(s)
Registration No. 39,107

Atty. Docket No. **P108341-09011**
1050 Connecticut Avenue, NW, Suite 600
Washington, D.C. 20036-5339
(202) 638-5000

RJB:ccd